

REMARKS

Claims 32-37, 39-62 and 71-116, and 118-125 are pending in the instant application. Claims 32-37, 39, 40, 42, 44-62, 115, 116, 118, and 119 are allowed. Claims 41, 43, 71-81, and 93-114 stand rejected. Claims 82-92 are objected to. The specification is objected to. Claims 41, 43, 71-114 are amended herein. Claims 126-141 are added herein. Support for new and amended claims can be found at page 5, line 25 through page 6, line 13, page 9, line 31 through page 11, line 30, page 12, lines 11-13 and at page 12, lines 28-32 of the specification. Thus, no new matter has been added.

SPECIFICATION OBJECTION

The specification is objected to for allegedly failing to provide proper antecedent basis for the claimed subject matter. The Examiner suggests the insertion of an additional sentence disclaiming saponin-derived immunostimulants at the end of the last paragraph of page 5 to overcome the objection. The Examiner also notes that this objection is not based on a written description requirement but alleges that the application "provide antecedent bases for claim language. See 37 CFR 1.75(d)(1) and MPEP 608.01(o)." Applicant respectfully traverses this objection.

Applicant respectfully submits that both 37 CFR 1.75(d)(1) and MPEP 608.01(o) require that the claims find support in the description so that the "meaning of the terms in the claims may be ascertainable." 37 CFR 1.75(d)(1). However, neither the CFR nor the MPEP requires a verbatim recitation of the claim language within the specification. Furthermore, the Federal Circuit has held that the failure to provide "explicit antecedent basis for terms does not always render a claim indefinite." *Bose Corp. v. JBL, Inc.*, 274 F.3d 1354, 1359 (Fed. Cir. 2001). Citing the MPEP 2173.05(e) (6th ed. Rev. 1 Sept. 1995), the court quoted that "If the scope of a claim would be reasonably ascertainable by those skilled in the art then the claim is not indefinite." *Id.* In addition, the court cited *Ex parte Porter*, 25 U.S.P.Q.2D 1144, 1146 (Bd. Pat. Apps. & Int. 1992) and *In re Moore*, 58 C.C.P.A. 1042, 439 F.2d 1232, 1235, 169 U.S.P.Q.236, 238 (CCPA 1971), "The definiteness of the language employed must be analyzed--not in a vacuum, but always in light of the teachings of the prior art and of the particular application disclosure as it would be interpreted by one possessing the ordinary level of skill in the pertinent art." *Id.*

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Applicant further submits that:

The function of the description requirement is to ensure that the inventor had possession, as of the filing date of the application relied on, of the specific subject matter later claimed by him. To comply with the description requirement it is not necessary that the application describe the claimed invention in *ipsis verbis*; all that is required is that it reasonably convey to persons skilled in the art that, as of the filing date thereof, the inventor had possession of the subject matter later claimed by him

In re Edwards, 568 F.2d 1349 at 1351-52, 196 U.S.P.Q. 465 at 467 (CCPA 1978) (citations omitted). Thus, the court in *Edwards* states explicitly that the phrasing of the claims need not be reiterated word for word in the specification.

Applicant further submits that:

If...the specification contains a description of the claimed invention, albeit not in *ipsis verbis* (in the identical words), then the examiner or Board, in order to meet the burden of proof, must provide reasons why one of ordinary skill in the art would not consider the description sufficient.

In re Alton, 76 F.3d 1168, 1175, 37 USPQ2d 1578, 1583 (Fed. Cir.1996).

Applicant respectfully submits that the specification discloses in several places various examples of immunostimulants, including Quil A, which is described as a "saponin preparation isolated from the South American tree *Quilaja Saponaria Molina* and was first described by Dalsgaard *et al.* in 1974 ("Saponin adjuvants", Archiv. für die gesamte Virusforschung, Vol. 44, Springer Verlag, Berlin, p243-254)." See page 6 of the specification. Thus, Applicant not only provides a definition of saponin within the specification, but also provides a reference indicating that saponin is a term understood in the art. As discussed above, it is not necessary to describe the claimed invention in *ipsis verbis*. More importantly it is not necessary to amend the description as the Examiner suggests to include verbatim terms from the claims. Applicant, thus invites the Examiner to provide reasons why one of ordinary skill in the art would not understand the proviso of claim 32 "wherein the immunostimulant is not a saponin derived from the bark of *Quillaja Saponaria Molina*," when Applicant has clearly provided a definition of saponin in the specification.

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The specification is also objected to for the term “RTS” on line 13 of page 12. Applicant would like to clarify that RTS,S is a mixed particle antigen which comprises two polypeptides – a hybrid antigen (RTS) and the hepatitis B surface antigen (S), for further information see page 5 lines 16-26 of WO93/10152 which is referred to at page 12 of the specification. In addition, RTS is itself is a hybrid antigen composed of a portion of the circumsporozoite protein of *Plasmodia falciparum* attached to a segment of the hepatitis B surface antigen (S), see page 3 of WO93/10152 for further information. Hence, the term “RTS,” as used in line 13 page 12, correctly refers to the *P. falciparum*/hepatitis B hybrid antigen, RTS.

CLAIM OBJECTIONS

Claims 71-81 are objected to for the informality of identifying LnRh(GnRH) as an antigen and not identifying it by its complete name. Applicant has amended claims 41, and 71-81 herein to recite "luteinizing hormone-releasing hormone (gonadotropin-releasing hormone)" in place of "LnRh(GnRH)." Applicant respectfully submits that the term LnRh(GnRH) is well known in the art as the abbreviation of luteinizing hormone-releasing hormone (gonadotropin-releasing hormone). Applicant has also amended the specification to include the full name of this term at page 12 of the specification. Furthermore, Applicant includes herein a hardcopy printout of Locus Link PubMed Search, <http://www.ncbi.nlm.nih.gov>, which provides various aliases for luteinizing hormone-releasing hormone (gonadotropin-releasing hormone), including abstracts published prior to filing that use the terms “LnRH” “LHRH” and/or “GnRH” to describe luteinizing hormone-releasing hormone (gonadotropin-releasing hormone).

35 U.S.C. §112, FIRST PARAGRAPH

Claims 41, 43, 71-81 and 93-114 stand rejected under 35 U.S.C. §112, first paragraph. The Examiner alleges that, “while being enabling for immunogenic compositions” the specification “does not reasonably provide enablement for vaccines against all of the identified pathogens.” In particular, the Examiner alleges that these claims still read on “vaccines” despite previous amendments made to these claims.

Applicant has amended claim 41 to recite an immunogenic composition rather than a vaccine. Support for amended claim 41 can be found, for example, at page 9, lines 31-32, page

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14, lines 9-15, and Example 2 starting on page 17 of the specification. In addition, Applicant has amended claim 43 so it no longer depends from amended claim 41. Furthermore, Applicant herein adds claims 126-137 which are directed to immunogenic compositions, and Applicant amends claims 71-81, as suggested by the Examiner, to depend from claims 127-137, respectively. In addition, Applicant has amended claims 71-81 to include the following additional antigens:

RTS,S, *P. faciparum* MSP1, *P. faciparum* AMA1, *P. faciparum* MSP3, *P. faciparum* EBA, *P. faciparum* GLURP, *P. faciparum* RAP1, *P. faciparum* RAP2, *P. faciparum* Sequestrin, *P. faciparum* PfEMP1, *P. faciparum* Pf332, *P. faciparum* LSA1, *P. faciparum* LSA3, *P. faciparum* STARP, *P. faciparum* SALSA, *P. faciparum* PfEXPa, *P. faciparum* Pfs25, *P. faciparum* Pfs28, *P. faciparum* PFS27/25, *P. faciparum* Pfs16, *P. faciparum* Pfs48/45, *P. faciparum* Pfs230, and any analogues of *P. faciparum* antigens from *Plasmodium* ssp

Support for new claims 126-137 and amended claims 71-81 can be found at page 9, line 31 through page 11, line 30 and page 12, lines 20-28 of the specification. Furthermore, Applicant has amended claims 82-114 to depend from one of claims 42-52. Finally, Applicant has amended claims 93-103 to recite a vaccine composition wherein the "antigen is RTS,S." Support for amended claims 93-103 can be found, for example, at page 12, lines 11-13 of the specification.

Applicant has also added new claims 138-141 herein. New claim 138 recites:

An adjuvant composition comprising an immunostimulant adsorbed onto a metallic salt particle, wherein the metallic salt particle is substantially free of antigen and wherein the immunostimulant is selected from the group consisting of: bacterial derived compound, immunostimulatory oligonucleotide, block copolymer, cholera toxin, and immunostimulatory cytokine.

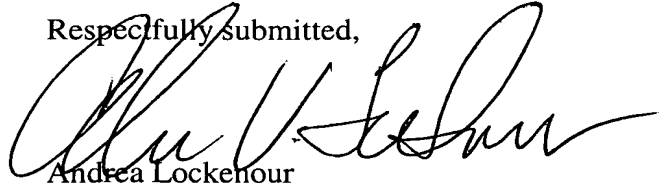
Support for new claims 138-141 can be found at page 5, line 25 through page 6 line 13 as well as page 6, lines 28-32.

Applicant respectfully submits that in view of the forgoing remarks and the claims as amended, the Applicant has overcome the Examiner's rejection under 35 U.S.C. §112, first paragraph, and that rejection should be withdrawn.

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If it would expedite the prosecution of this application, the Examiner is invited to confer with the Applicant's undersigned attorney.

Respectfully submitted,

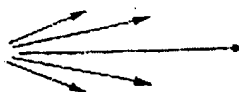
A handwritten signature in black ink, appearing to read 'Andrea Lockenour', written over the typed name.

Andrea Lockenour
Attorney for Applicant
Registration No. 51,962

GLAXOSMITHKLINE
Corporate Intellectual Property - UW2220
P.O. Box 1539
King of Prussia, PA 19406-0939
Phone (610) 270-7568
Facsimile (610) 270-5090
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LocusLink



PubMed Entrez
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BLAST

OMIM

Map Viewer

Taxonomy

Structure

Display Brief

Organism: All

Query:

Go

Clear

View Hs GNRH1

One of 1 Loci

Save All Loci

A B C D E F G H I J K L M N O P Q R S T U V W X Y Z

LocusLink will be replaced by Entrez Gene. Check Gene FAQ for current information.

Click to Display mRNA-Genomic Alignments (spanning 5143 bps)

Gene	PUB	GENE	ACEVIEW	UNIGENE	VAR	HOMOL
GDB	e!	UCSC				

Homo sapiens Official Gene Symbol and Name (HGNC)

GNRH1: gonadotropin-releasing hormone 1 (leutinizing-releasing hormone)

LocusID: 2796

Overview

?

LocusLink Home

Locus Type: gene with protein product, function known or inferred

GNRH1 Index:

Product: gonadotropin-releasing hormone 1 (leutinizing-releasing hormone)

Top of Page

Nomenclature

Alternate Symbols: GRH, GNRH, LHRH, LNRH

Overview

Function

Alias: gonadotropin-releasing hormone 1 (lutienizing hormone-releasing hormone)

Relationships

Map

RefSeq

Function [Submit GeneRIF](#) [\(All Pubs\)](#)

Related Seqs

Links

Please note: As a consequence of our transition to Entrez Gene, GeneRIFs will only be displayed in the Entrez Gene record for this locus. [Gene](#)

?

LocusLink:

Collaborators

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RefSeq:

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Statistics

Gene Ontology™:

Term	Evidence	Source	Pub
• cell-cell signaling	TAS	GOA	pm
• development	TAS	GOA	pm
• extracellular	IEA	GOA	
• luteinizing hormone-releasing factor activity	TAS	GOA	pm
• negative regulation of cell proliferation	TAS	GOA	pm
• signal transduction	TAS	GOA	pm
• soluble fraction	TAS	GOA	pm

?

Relationships
Rat Homology Map Viewer

Map Information

Chromosome:	8		?
			mv
Cytogenetic:	8p21-p11.2	HUGO	
Markers:	Chr. 8	<u>D8S1916</u> D8S1916	mv
		<u>WI</u>	
	Chr. 8	=	mv
		<u>18854</u>	
		<u>SHGC</u>	
	Chr. 8	=	mv
		<u>31262</u>	

NCBI Reference Sequences (RefSeq)

Category: PROVISIONAL

mRNA:	<u>NM_000825</u>	
Protein:	<u>NP_000816</u> gonadotropin-releasing hormone 1 (leutinizing-releasing hormone)	BL
GenBank	<u>X01059</u>	
Source:		

Category: NCBI Genome Annotation

Genomic	<u>NT_023666</u>	gb sv mv ev mm
Contig:		
Haplotype	reference	
Annotation for this locus:		
Evidence:	supported by alignment with mRNA	
mRNA:	<u>NM_000825</u>	
Protein:	<u>NP_000816</u>	BL

Related Sequences

Nucleotide	Type	Protein	
<u>X15215</u>	g	<u>CAA33285</u>	BL
<u>BC067290</u>	m		
<u>M12578</u>	m	<u>AAA35916</u>	BL
<u>X01059</u>	m	<u>CAA25526</u>	BL
None	p	<u>P01148</u>	BL

Additional Links

- **OMIM:** 152760
- **UniGene:** Hs.82963
- **KEGG pathway:** Neuroactive ligand-receptor interaction

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Gene summary	Expression level , number of transcript variants and protein
AceView inferences	Number of introns , their type and feet*
... Transcripts and sequences	Alternative features : about promoters, cassettes and prote
... Proteins	*: data derived from AceView analysis
Introns and exons	
cDNA clones	
Bibliography	
Diagram	

Homo sapiens gene GNRH1 encoding gonadotropin-releasing hormone 1 (leutinizing-releasing hormone).

GENE SUMMARY ↑ ?

Alias names and map on chromosome 8 ↑ ?

This gene GNRH1, also known as GRH, GNRH, LHRH, LNRH or 8_25306006, maps on chromosome 8, at 8p21-p11.2 according to HUGO. It covers 7.32 kb, from 25306006 to 25298686 (NCBI build 34, August 2003), on the reverse strand.

Products ↑ ?

It encodes a set of "progonadoliberin i".

Molecular properties: gonadotropin-releasing hormone 1 (lutienizing hormone-releasing hormone).

Description of the protein family.

The Gonadotropin-releasing hormone motif is found in 4 isoforms from this gene. 1 other gene (GNRH2) in the database also contains this motif.

[InterPro annotation] The gonadotropin-releasing hormones (GnRH)

(gonadoliberin) are a family of peptides that play a pivotal role in reproduction.

The main function of GnRH is to act on the pituitary to stimulate the synthesis and secretion of luteinizing and follicle-stimulating hormones, but GnRH also acts on the brain, retina, sympathetic nervous system, gonads and placenta in certain species. There seems to be at least three forms of GnRH. The second form is expressed in midbrain and seems to be widespread. The third form has only been found so far in fish. GnRH is a C-terminal amidated decapeptide processed from a larger precursor protein. Four of the ten residues are perfectly conserved in all species where GnRH has been sequenced.

Phenotype ↑ ?

Interesting annotations are available from OMIM 152760.

Functional annotation ↑ ?

From LocusLink Proteome or GOA annotation, the products would have luteinizing hormone-releasing factor activity, would be involved in negative regulation of cell proliferation, development, signal transduction, cell-cell signaling and would localize in soluble fraction, extracellular. In addition, from Pfam homology, the products would have hormone activity.

The following table summarizes the phenotype and function of this gene and provides links to other genes in the same species with similar annotations:

Type		
OMIM	gnrh	OMIM
Function	negative regulation of cell proliferation	LocusLink
	development	
	signal transduction	
	cell-cell signaling	
	luteinizing hormone-releasing factor activity	LocusLink
	hormone activity	Pfam
Localisation	soluble fraction	LocusLink
	extracellular	

Expression level and number of variants ↑ ?

According to AceView, this gene is expressed at high level.

The sequence of this gene is supported by 39 sequences from 34 cDNA clones and produces, by alternative splicing, 4 different transcripts aDec03, bDec03, cDec03, dDec03 altogether encoding 2 different protein isoforms.

Introns ↑ ?

The gene contains 4 confirmed introns, 2 of which are alternative. Comparison to the genome sequence shows that 4 introns follow the consensual [gt-ag] rule. See this **table** for details.

Alternative features ↑ ?

There are 2 probable alternative promoters. The transcripts appear to differ by common exons with different boundaries, because an internal intron is not always spliced out.

MOLECULES ↑

According to our analysis, this gene produces, by alternative splicing, 4 types of transcripts, predicted to encode 2 distinct proteins.

Transcripts and sequences ↑ ?

Any sequence described in this table can be accessed by clicking the bp value. In the first column, the first sequence available for the transcript is derived from the genome. When available, the AM AceView consensus sequence of the mRNA, where preference was given to a cDNA clone matching the genome, is given underneath. The premessenger sequence is in the column Transcription Unit, and the 5 kb sequence upstream of the transcription unit is also available from there. UTR sequences are also provided. For computer oriented people, we also provide a FASTA sequence page ?

Variant	5' UTR	3' UTR	# exons	# clones	Transcription unit	coordinates on gene
aDec03 2014bp	1468bp	159bp, polyA	4	6	6516bp. 5 kb just upstream	806 to 7321
bDec03 2287bp	1741bp	159bp, polyA	5	6	7321bp. 5 kb just upstream	1 to 7321
cDec03 2883bp AM_2887bp	2433bp	159bp, polyA	3	32	6516bp. 5 kb just upstream	806 to 7321
dDec03 3156bp AM_3160bp	2706bp	159bp, polyA	4	32	7321bp. 5 kb just upstream	1 to 7321

PROTEINS↑

Annotation of variants ↑ ?

mRNA variant	Overview (for structural details see previous table)
aDec03	This complete CDS mRNA is 2014 bp long. We annotate here the sequence derived from the genome, although the best path through the available clones differs from it in 26 positions. It has 4 exons. It has a very long 5' UTR. The premessenger covers 6.52 kb on the NCBI build 34, August 2003 genome. The protein (128 aa, 14.6 kDa, pI 8.8) contains one Gonadotropin-releasing hormone motif. It also contains an ER membrane domain [Psort2]. Taxblast (threshold 10 ⁻³) tracks ancestors down to Teleostomi.
bDec03	This complete CDS mRNA is 2287 bp long. We annotate here the sequence derived from the genome, although the best path through the available clones differs from it in 26 positions. It has 5 exons. It has a very long 5' UTR. The premessenger covers 7.32 kb on the NCBI build 34, August 2003 genome. The protein (128 aa, 14.6 kDa,

	pI 8.8) contains one Gonadotropin-releasing hormone motif. It also contains an ER membrane domain [Psort2]. Taxblast (threshold 10 ⁻³) tracks ancestors down to Teleostomi.
cDec03	This complete CDS mRNA is 2883 bp long. We annotate here the sequence derived from the genome, although the best path through the available clones differs from it in 6 positions. It has 3 exons. It has a very long 5' UTR. The premessenger covers 6.52 kb on the NCBI build 34, August 2003 genome. The protein (96 aa, 10.8 kDa, pI 6.7) contains one Gonadotropin-releasing hormone motif. It also contains an ER membrane domain [Psort2]. Taxblast (threshold 10 ⁻³) tracks ancestors down to Teleostomi.
dDec03	This complete CDS mRNA is 3156 bp long. We annotate here the sequence derived from the genome, although the best path through the available clones differs from it in 6 positions. It has 4 exons. It has a very long 5' UTR. The premessenger covers 7.32 kb on the NCBI build 34, August 2003 genome. The protein (96 aa, 10.8 kDa, pI 6.7) contains one Gonadotropin-releasing hormone motif. It also contains an ER membrane domain [Psort2]. Taxblast (threshold 10 ⁻³) tracks ancestors down to Teleostomi.

Proteins ↑ ?

This table allows to see at a glance from the last column if an isoform has its exonic structure fully supported by a single clone, or if it requires concatenation of two or more cDNA clones.

Protein & sequence		Extends from	coordinates on mRNA	minimal set of supporting clones
aDec03 128aa	complete	Met to Stop	1469 to 1855	M12578 W05214
bDec03 128aa	complete =a	Met to Stop	1742 to 2128	M12578 W05214
cDec03 96aa	complete	Met to Stop	2434 to 2724	X01059
dDec03 96aa	complete =c	Met to Stop	2707 to 2997	X01059

Intron exon structure and support ↑ ?

Sequences of exons and introns are available by clicking on the lengths in column 3.

	in variant	Length & DNA	Coordinates on gene	Supporting clone (s)

Exon 1	b,d	288bp	1 to 288	AL706041
Alternative intron [gt-ag]	b,d	532bp	289 to 820	AL706041
Alternative exon 2	a	1575bp	806 to 2380	
Alternative exon 3	c	2586bp	806 to 3391	
Alternative exon 4	b	1560bp	821 to 2380	
Alternative exon 5	d	2571bp	821 to 3391	
Alternative intron [gt-ag]	a,b	869bp	2381 to 3249	M12578
Alternative exon 6	a,b	142bp	3250 to 3391	M12578
Intron [gt-ag]	a,b,c, d	1521bp	3392 to 4912	NM_000825 and 10 others
Exon 7	a,b,c, d	96bp	4913 to 5008	NM_000825 and 10 others
Intron [gt-ag]	a,b,c, d	2112bp	5009 to 7120	H38517 and 13 others
Exon 8	a,b,c, d	201bp	7121 to 7321	NM_000825 and 9 others

Main supporting clones for gene GNRH1 ↑ ?

This table shows the minimal list of clones necessary to reconstruct the set of AceView reference mRNAs (AM). Each AM sequence is a "golden path" composite of cDNAs, where we choose, for each segment, the clone compatible with the intron structure of the variant that best matches the genome. The next table shows the alignments of the NCBI reference sequences (NM). The table of all clones is elsewhere.

Sequence	Tissue	match over #bp (% length)	# differences (% id)	Gene and transcript	Properties
M12578	hypothalamus	470 bp (100%)	no error (100%id)	GNRH1.a, b	complete CDS
X01059		1511 bp (100%)	4 err (99.7% id)	GNRH1.c, d	
AL706041	human skeletal muscle	528 bp (100%)	no error (100%id)	GNRH1.b, d	
AW978675		625 bp (98%)	12 err (98.1%id)	GNRH1.c, d	
AI457202		459 bp (100%)	no error (100%id)	GNRH1.a, c	complete
W05214	lung	114 bp	no error	GNRH1.a,	

		(100%)	(100%id)	b, c, d	CDS
CB269203		647 bp (100%)	4 err (99.4% id)	GNRH1.a, b, c, d	
BG540893		620 bp (98%)	26 err (95.9%id)	GNRH1.a, b, c, d	

RefSeq clones supporting gene GNRH1 ↑ ?

Sequence	match over #bp (% length)	# differences (% id)	Gene and transcript	Properties
NM_000825	1511 bp (100%)	4 err (99.7%id)	GNRH1.c, d	complete CDS

BIBLIO abstracts and RIFs↑

- J Clin Endocrinol Metab 2003 Jun;88(6):2730-7. Autosomal recessive idiopathic hypogonadotropic hypogonadism: genetic analysis excludes mutations in the gonadotropin-releasing hormone (GnRH) and GnRH receptor genes. ***Genetic analysis has excluded sequence variations in GNRH1 and GNRHR in four families with recessive IHH, suggesting the existence of a novel, as-yet-undiscovered gene for this condition.***
- Nat Med 2002 Dec;8(12):1421-6. The neuropeptides GnRH-II and GnRH-I are produced by human T cells and trigger laminin receptor gene expression, adhesion, chemotaxis and homing to specific organs. ***GnRH-II and GnRH-I interact directly with T cells and trigger gene transcription, adhesion, chemotaxis and homing to specific organs, which may be of clinical relevance.***
- Biochem Biophys Res Commun 2002 May 31;294(1):11-5. Luteinizing hormone-releasing hormone induces JunD-DNA binding and extends cell cycle in human ovarian cancer cells. ***JunD activated by LHRH acts as a modulator of cell proliferation and cooperates with the anti-apoptotic and anti-mitogenic functions of LHRH.***
- Mol Endocrinol 2002 Jun;16(6):1145-53. Coupling of GnRH concentration and the GnRH receptor-activated gene program. ***Coupling of GnRH concentration and the GnRH receptor-activated gene program***
- Mol Endocrinol 2002 Mar;16(3):435-49. Identification of a discrete promoter region of the human GnRH gene that is sufficient for directing neuron-specific

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